REMARKS

Applicants have amended the title to more specifically describe the invention. Submitted herewith is a response to the Notice to Comply, which amends the specification to include a copy of the sequence listing.

Applicants have cancelled Claim 6 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 1 to remove reference to the Figure and to recite that the claimed antibody specifically binds to the polypeptide of SEQ ID NO: 30. Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed June 3, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Specification:

The PTO has objected to the title as not being descriptive. Applicants have amended the title herein.

The PTO has stated that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). The PTO states that the application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 because the application does not contain, as a separate part of the disclosure on a paper copy, a "Sequence Listing" as required by 37 C.F.R. § 1.821(c).

Applicants submit herewith a response to the Notice to Comply which amends the specification to include a paper copy of the "Sequence Listing," which is also submitted herewith.

IDS:

The PTO has requested additional information on the references cited in the BLAST results reported in the Information Disclosure Statement filed September 10, 2002. Applicants submit herewith more detailed information regarding the cited sequences (attached as Exhibit 1).

Priority Determination:

The PTO has stated that because the claimed antibodies have no utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 2, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/098749 filed 9/1/1998.

Applicants submit that for the reasons stated below, the claimed antibodies have a credible, substantial, and specific utility. The sequences of SEQ ID NOs: 29 and 30 were first disclosed in US Provisional Application 60/098749 filed 9/1/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-6 as lacking a specific, substantial, and credible utility. The PTO asserts that there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO831. One of the asserted utilities for the claimed antibodies is use as a diagnostic tool based on the data that PRO831 cDNA is more highly expressed in normal lung

tissue and kidney tumor compared to lung tumor and normal kidney tissue, respectively. The PTO has rejected this utility because there is no supporting evidence to indicate that the polypeptides encoded by the disclosed polynucleotide of the instant invention are more highly expressed in some normal and tumor tissue compared to their tumor and normal counterparts.

The PTO also asserts that the evidence that the polynucleotide is more highly expressed in kidney tumor and normal lung is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to normal kidney and lung tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. The PTO asserts that without knowing the identity of the tumor, one of skill in the art cannot use the proteins or their antibodies for diagnostic or therapeutic purposes. The PTO also states that the specification does not disclose a correlation between any specific disorder and the altered level of the disclosed polypeptides, or predict whether the polypeptides would have high or low expression in specific, diseased tissue compared to healthy tissue control. The PTO also argues that because the normal tissue and tumor samples were from different humans, there is no possibility of direct comparison between the two. The PTO also states that because cancerous tissue is aneuploid, the data is unreliable. Finally the PTO argues that there is no necessary correlation between protein expression and nucleic acid levels.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must

be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the Gene Encoding the PRO831 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the evidence of higher expression of the gene encoding the PRO831 polypeptide in normal lung and kidney tumor compared to lung tumor and normal kidney tissue is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to normal kidney and lung tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. Applicants also address the PTO's argument that because the normal tissue and tumor samples were from different humans, there is no possibility of direct comparison between the two, and that because cancerous tissue is aneuploid, the data is unreliable. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed antibodies.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 2). In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Contrary to the PTO's assertions that this makes the data unreliable, Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to

differentiate tumor from normal." He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO also argues that because cancerous tissue can be aneuploid, and the data in the instant application was not corrected for aneuploidy, "[a] slight amplification of a gene does not necessarily mean overexpression in a tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action at 6. The PTO relies on a single reference, Sen, 2000, Curr. Opin. Oncol. 12:82-88 (hereinafter Sen).

Applicants agree that Sen teaches that most cancerous tissues are aneuploid, and that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells tested. However, Applicants fail to see how it is relevant to the utility of the disclosed polypeptides or their antibodies whether the differential expression reported in Example 18 is due to aneuploidy or not. Regardless of whether the differential expression of the gene encoding PRO831 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in kidney tumor and normal lung compared to normal kidney tissue and lung tumor, respectively, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer. As discussed below, this fact leads to utility for the encoded polypeptides and their antibodies.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO argues that there is no supporting evidence that the polypeptide encoded by the nucleotide of the instant invention is more highly expressed in the normal tissue compared to the tumor tissue. The PTO also states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. Relying on Pennica *et al.*, 1998, PNAS USA 95:14717-14722

(hereinafter Pennica), the PTO states that the data pertaining to PRO831 polynucleotides do not necessarily indicate anything significant regarding the claimed PRO831 polypeptides.

Applicants respectfully submit that the PTO is confusing the relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased expression of a gene or mRNA expression on the other. The PTO focuses on the statement from Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 7-8. As an aside, it should be noted that this result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding PRO831 in kidney tumor compared to the normal kidney tissue and normal lung tissue compared to lung tumor tissue. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 3). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As

stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 4), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO831 mRNA is expressed at a higher level in kidney tumor compared to normal kidney tissue, and normal lung tissue compared to lung tumor tissue, the PRO831 polypeptide will also be expressed at a higher level in kidney tumor compared to normal kidney tissue, and normal lung tissue compared to lung tumor tissue. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer

cells compared to the corresponding normal tissue would have utility as a diagnostic tool, as would its antibodies. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of claimed antibodies as a cancer diagnostic tool.

The Claimed Antibodies would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO831, which Applicants submit is not true, an antibody to a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 3, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 5), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 6). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However,

even when this is not the case, an antibody to a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed polypeptides.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertions that there is no biological activity, expression pattern, phenotype, disease of condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO831. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO831 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene encoding the PRO831 polypeptide is more highly expressed in kidney tumor compared to normal kidney tissue, and normal lung tissue compared to lung tumor tissue. These data are strong evidence that the PRO831 polypeptide is associated with kidney and lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO831 polypeptide with a specific disease. This is a specific utility – it is not a general utility that would apply to the broad class of polypeptides and their antibodies.

Conclusion

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO831 gene in certain cancers is not reliable; and, (2) that because there is no necessary correlation between gene amplification and protein expression, the claimed antibodies cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO831 gene in kidney tumor compared to normal kidney tissue, and normal lung tissue compared to lung tumor tissue, are real and significant. This declaration also

indicates that given the relative difference in expression levels, the claimed antibodies have utility as cancer diagnostic tools. Applicants have also shown that whether the differential expression of the PRO831 polypeptide is due to aneuploidy or not does not affect the usefulness of the claimed antibodies as a diagnostic tool.

Next, the Applicants have shown that the reference cited by the PTO to support its conclusion that there is no necessary correlation between the level of gene expression and mRNA or protein expression does not support the PTO's position. Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the claimed antibodies have utility as a diagnostic tool for cancer.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, the PTO asserts that there is no asserted specific utility because there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature associated with PRO831. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because PRO831 is differentially expressed in certain cancer tissue compared to the corresponding normal tissue. This is not a general utility that would apply to the broad class of antibodies.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "specifically binds", stating that it is a relative term that renders the claim indefinite. The PTO argues that specifically is not defined in the claims and the specification does not provide a standard for ascertaining the requisite degree of binding. The PTO also argues that because some level of specificity is implicit in all the claims, the difference between "binds" and "binds specifically" cannot be determined.

Claim 6 has been cancelled and Claim 1 amended to recite "specifically binds". Applicants submit that the term "specifically binds" has a well established meaning – it refers to the binding of an antibody to a particular polypeptide, where the antibody does not substantially bind to any other polypeptide. One of skill in the art would readily understand the language of the claims to mean that the claimed antibodies bind to specifically defined polypeptides (in this case the polypeptides of SEQ ID NO: 30) but do not substantially bind to any other polypeptides. Since claim terms should be given their ordinary, art-recognized meaning, Applicants submit the present rejection is misplaced, and request that it be withdrawn.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO rejects Claims 1-6 as anticipated under 35 U.S.C. § 102(b) by Bergsma *et al.* (U.S. Patent No. 6,001,963), which issued December 14, 1999. The PTO states that because no disclosure to which priority is claimed meets the requirements of §§101 and 112, first paragraph, priority is set at the instant filing date, May 2, 2002. The PTO asserts that amino acids 14-22 of

SEQ ID NO: 2 of Bergsma have 100% identity to amino acids 5-13 of SEQ ID NO: 30. The PTO states that an antibody to this sequence will bind specifically to SEQ ID NO: 30 of the instant application. Applicants submit that Bergsma is not prior art under 35 U.S.C. § 102(b), and does not anticipate Claims 1-5 because it fails to teach each and every element of the claimed invention.

To anticipate under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication "more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Applicants submit that Bergsma is not prior art under 35 U.S.C. § 102(b) because it was not published more than one year prior to the date of the instant application for patent in the United States. The sequences of SEQ ID NOs: 29 and 30 were first disclosed in US Provisional Application 60/098749 filed 9/1/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants are entitled to a priority date of at least **August 24, 2000**. Bergsma issued on December 19,1999, less than one year prior to August 24, 2000. Thus Bergsma is not available as prior art under 102(b) against the instant application, and Applicants request that the PTO reconsider and withdraw the anticipation rejection under 35 U.S.C. §102(b).

Even if Bergsma is available as prior art, it does not anticipate Claims 1-5 of the instant invention. Under 35 U.S.C. §102(b), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). As amended, Claim 1, and dependent Claims 2-5, require that the antibody specifically bind to the polypeptide of SEQ ID NO: 30.

While Bergsma discusses the possibility of antibodies to fragments of the disclosed sequences, it does not explicitly disclose an antibody to the fragment consisting of amino acids 14-22 of SEQ ID NO: 2. Where an element of a claims is not explicitly disclosed, it can inherently be disclosed if must necessarily follow from the disclosure. As a fragment consisting of amino acids 14-22 of SEQ ID NO: 2 is not disclosed, and there is no reason for one of skill in the art to select such a fragment, an antibody to amino acids 14-22 of SEQ ID NO: 2 is not inherent in the disclosure. If one were to inject the polypeptide of SEQ ID NO: 2 into an animal

to generate antibodies, it does not necessarily follow that an antibody to amino acids 14-22 of SEQ ID NO: 2 would be generated, since there is no indication that that epitope would be available. Thus, Bergsman does not explicitly or inherently teach an antibody which specifically binds to SEQ ID NO: 30 of the instant application. For this reason, applicants request that the PTO reconsider and withdraw the anticipation rejection under 35 U.S.C. §102(b) based on Bergsma.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 2, 2004

By: _____

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